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| NEWS 2 | Jan 25 | BLAST(R) searching in REGISTRY available in STN on the Web |
| NEWS 3 | Jan 29 | FSTA has been reloaded and moves to weekly updates |
| NEWS 4 | Feb 01 | DKILIT now produced by FIZ Karlsruhe and has a new update frequency |
| NEWS 5 | Feb 19 | Access via Tymnet and SprintNet Eliminated Effective 3/31/02 |
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| NEWS 20 | Jun 10 | MEDLINE Reload |
| NEWS 21 | Jun 10 | PCTFULL has been reloaded |

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| NEWS EXPRESS | February 1 CURRENT WINDOWS VERSION IS V6.0d, CURRENT MACINTOSH VERSION IS V6.0a(ENG) AND V6.0Ja(JP), AND CURRENT DISCOVER FILE IS DATED 05 FEBRUARY 2002 |
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=> s antibody'
THIS COMMAND NOT AVAILABLE IN THE CURRENT FILE
Some commands only work in certain files.  For example, the EXPAND
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index.  Enter "HELP COMMANDS" at an arrow prompt (=>) for a list of
commands which can be used in this file.

=> s antibody
THIS COMMAND NOT AVAILABLE IN THE CURRENT FILE
Some commands only work in certain files.  For example, the EXPAND
command can only be used to look at the index in a file which has an
index.  Enter "HELP COMMANDS" at an arrow prompt (=>) for a list of
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=> file medline embase biosis scisearch caplus
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                                                   ENTRY    SESSION
FULL ESTIMATED COST                                 0.21       0.21

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=> s antibod?
L1     2317334 ANTIBOD?

=> s l1 and immunoglobulin
L2      335495 L1 AND IMMUNOGLOBULIN

=> s l2 and RhD
L3         197 L2 AND RHD

=> s l3 and inhibit ADCC
L4           0 L3 AND INHIBIT ADCC

=> s l3 and mutation
L5           8 L3 AND MUTATION

=> s l5 and constant region
L6           5 L5 AND CONSTANT REGION

=> dup remove l6
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PROCESSING COMPLETED FOR L6
L7 1 DUP REMOVE L6 (4 DUPLICATES REMOVED)

=> d l7 cbib abs

L7 ANSWER 1 OF 1 MEDLINE DUPLICATE 1
1999388014 Document Number: 99388014. PubMed ID: 10458776. Recombinant human IgG molecules lacking Fcgamma receptor I binding and monocyte triggering activities. Armour K L; Clark M R; Hadley A G; Williamson L M. (Division of Immunology Department of Pathology, University of Cambridge, Cambridge, GB. ) EUROPEAN JOURNAL OF IMMUNOLOGY, (1999 Aug) 29 (8) 2613-24. Journal code: 1273201. ISSN: 0014-2980. Pub. country: GERMANY: Germany, Federal Republic of. Language: English.
AB Subclasses of human IgG have a range of activity levels with different effector systems but each triggers at least one mechanism of cell destruction. We are aiming to engineer non-destructive human IgG **constant regions** for therapeutic applications where depletion of cells bearing the target antigen is undesirable. The attributes required are a lack of killing via Fcgamma receptors (R) and complement but retention of neonatal FcR binding to maintain placental transport and the prolonged half-life of IgG. Eight variants of human IgG **constant regions** were made with anti-**RhD** and CD52 specificities. The **mutations**, in one or two key regions of the CH2 domain, were restricted to incorporation of motifs from other subclasses to minimize potential immunogenicity. IgG2 residues at positions 233 - 236, substituted into IgG1 and IgG4, reduced binding to FcgammaRI by 10(4)-fold and eliminated the human monocyte response to **antibody**-sensitized red blood cells, resulting in **antibodies** which blocked the functions of active **antibodies**. If glycine 236, which is deleted in IgG2, was restored to the IgG1 and IgG4 mutants, low levels of activity were observed. Introduction of the IgG4 residues at positions 327, 330 and 331 of IgG1 and IgG2 had no effect on FcgammaRI binding but caused a small decrease in monocyte triggering.

=> s "FOG1"
L8 36 "FOG1"

=> s l8 and antibody
L9 0 L8 AND ANTIBODY

=> dup remove l8
PROCESSING COMPLETED FOR L8
L10 16 DUP REMOVE L8 (20 DUPLICATES REMOVED)

=> d l10 1-16 cbib abs

L10 ANSWER 1 OF 16 MEDLINE DUPLICATE 1
2002083128 Document Number: 21668225. PubMed ID: 11809723. Different substitutions at residue D218 of the X-linked transcription factor GATA1 lead to altered clinical severity of macrothrombocytopenia and anemia and are associated with variable skewed X inactivation. Freson Kathleen; Matthijs Gert; Thys Chantal; Marien Paul; Hoylaerts Marc F; Vermylen Jos; Van Geet Chris. (Center for Molecular and Vascular Biology, University of Leuven, Leuven, Belgium. ) HUMAN MOLECULAR GENETICS, (2002 Jan 15) 11 (2) 147-52. Journal code: 9208958. ISSN: 0964-6906. Pub. country: England: United Kingdom. Language: English.
AB GATA1 is the X-linked transcriptional activator required for megakaryocyte and erythrocyte differentiation. Missense mutations in the N-terminal zinc finger (Nf) of GATA1 result in abnormal hematopoiesis, as documented in four families: the mutation V205M leads to both severe

macrothrombocytopenia and dyserythropoietic anemia, D218G to macrothrombocytopenia and mild dyserythropoiesis without anemia, G208S to macrothrombocytopenia and R216Q to macrothrombocytopenia with beta-thalassemia. The three first GATA1 mutants display a disturbed binding to their essential transcription cofactor **FOG1**, whereas the fourth mutant shows an abnormal direct DNA binding. In this study, we describe a new family with deep macrothrombocytopenia, marked anemia and early mortality, if untreated, due to a different GATA1 mutation (D218Y) in the same residue 218 also implicated in the above mentioned milder phenotype. Zinc finger interaction studies revealed a stronger loss of affinity of D218Y-GATA1 than of D218G-GATA1 for **FOG1** and a disturbed GATA1 self-association. Comparison of the phenotypic characteristics of patients from both families revealed that platelet and erythrocyte morphology as well as expression levels of the platelet GATA1-target gene products were more profoundly disturbed for the hemizygote D218Y mutation. The D218Y allele (as opposed to the D218G allele) was not expressed in the platelets of a female carrier while her leukocytes showed a skewed X-inactivation pattern. We conclude that the nature of the amino acid substitution at position 218 of the Nf of GATA1 is of crucial importance in determining the severity of the phenotype in X-linked macrothrombocytopenia patients and possibly also in inducing skewed X inactivation.

L10 ANSWER 2 OF 16 CAPLUS COPYRIGHT 2002 ACS
2001:471581 Document No. 135:150158 The friend of GATA proteins U-shaped, FOG-1, and FOG-2 function as negative regulators of blood, heart, and eye development in Drosophila. Fossett, Nancy; Tevosian, Sergei G.; Gajewski, Kathleen; Zhang, Qian; Orkin, Stuart H.; Schulz, Robert A. (Department of Biochemistry and Molecular Biology, Graduate Program in Genes and Development, The University of Texas M. D. Anderson Cancer Center, Houston, TX, 77030, USA). Proceedings of the National Academy of Sciences of the United States of America, 98(13), 7342-7347 (English) 2001. CODEN: PNASA6. ISSN: 0027-8424. Publisher: National Academy of Sciences.
AB Friend of GATA (FOG) proteins regulate GATA factor-activated gene transcription. During vertebrate hematopoiesis, FOG and GATA proteins cooperate to promote erythrocyte and megakaryocyte differentiation. The Drosophila FOG homolog U-shaped (Ush) is expressed similarly in the blood cell anlage during embryogenesis. During hematopoiesis, the acute myeloid leukemia 1 homolog Lozenge and Glial cells missing are required for the prodn. of crystal cells and plasmatocytes, resp. However, addnl. factors have been predicted to control crystal cell proliferation. In this report, the authors show that Ush is expressed in hemocyte precursors and plasmatocytes throughout embryogenesis and larval development, and the GATA factor Serpent is essential for Ush embryonic expression. Furthermore, loss of ush function results in an overprodn. of crystal cells, whereas forced expression of Ush reduces this cell population. Murine FOG-1 and FOG-2 also can repress crystal cell prodn., but a mutant version of FOG-2 lacking a conserved motif that binds the corepressor C-terminal binding protein fails to affect the cell lineage. The GATA factor Pannier (Pnr) is required for eye and heart development in Drosophila. When Ush, FOG-1, FOG-2, or mutant FOG-2 is coexpressed with Pnr during these developmental processes, severe eye and heart phenotypes result, consistent with a conserved neg. regulation of Pnr function. These results indicate that the fly and mouse FOG proteins function similarly in three distinct cellular contexts in Drosophila, but may use different mechanisms to regulate genetic events in blood vs. cardial or eye cell lineages.

L10 ANSWER 3 OF 16 MEDLINE DUPLICATE 2
2001469543 Document Number: 21405724. PubMed ID: 11514507. Three target genes for the transcriptional activator Cat8p of Kluyveromyces lactis: acetyl coenzyme A synthetase genes KlACS1 and KlACS2 and lactate permease

gene KlJEN1. Lodi T; Saliola M; Donnini C; Goffrini P. (Istituto di Genetica, Parco Area delle Scienze 11-A, Universita degli Studi di Parma, 43100 Parma, Italy. ) JOURNAL OF BACTERIOLOGY, (2001 Sep) 183 (18) 5257-61. Journal code: 2985120R. ISSN: 0021-9193. Pub. country: United States. Language: English.

AB The aerobic yeast Kluyveromyces lactis and the predominantly fermentative Saccharomyces cerevisiae share many of the genes encoding the enzymes of carbon and energy metabolism. The physiological features that distinguish the two yeasts appear to result essentially from different organization of regulatory circuits, in particular glucose repression and gluconeogenesis. We have isolated the KlCAT8 gene (a homologue of S. cerevisiae CAT8, encoding a DNA binding protein) as a multicopy suppressor of a **fog1** mutation. The **Fog1** protein is a homologue of the Snf1 complex components Gal83p, Sip1p, and Sip2p of S. cerevisiae. While CAT8 controls the key enzymes of gluconeogenesis in S. cerevisiae, KlCAT8 of K. lactis does not (I. Georis, J. J. Krijger, K. D. Breunig, and J. Vandenhaute, Mol. Gen. Genet. 264:193-203, 2000). We therefore examined possible targets of KlCat8p. We found that the acetyl coenzyme A synthetase genes, KlACS1 and KlACS2, were specifically regulated by KlCAT8, but very differently from the S. cerevisiae counterparts. KlACS1 was induced by acetate and lactate, while KlACS2 was induced by ethanol, both under the control of KlCAT8. Also, KlJEN1, encoding the lactate-inducible and glucose-repressible lactate permease, was found under a tight control of KlCAT8.

L10 ANSWER 4 OF 16 CAPLUS COPYRIGHT 2002 ACS

2001:863021 Document No. 136:117173 Friend of GATA-1 represses GATA-3-dependent activity in CD4+ T cells. Zhou, Meixia; Ouyang, Wenjun; Gong, Qian; Katz, Samuel G.; White, J. Michael; Orkin, Stuart H.; Murphy, Kenneth M. (Department of Pathology and Immunology, Department of Medicine, Washington University School of Medicine, St. Louis, MO, 63110, USA). Journal of Experimental Medicine, 194(10), 1461-1471 (English) 2001. CODEN: JEMEAV. ISSN: 0022-1007. Publisher: Rockefeller University Press.

AB The development of naive CD4+ T cells into a T helper (Th) 2 subset capable of producing interleukin (IL)-4, IL-5, and IL-13 involves a signal transducer and activator of transcription (Stat)6-dependent induction of GATA-3 expression, followed by Stat6-independent GATA-3 autoactivation. The friend of GATA (FOG)-1 protein regulates GATA transcription factor activity in several stages of hematopoietic development including erythrocyte and megakaryocyte differentiation, but whether FOG-1 regulates GATA-3 in T cells is uncertain. The authors show that FOG-1 can repress GATA-3-dependent activation of the IL-5 promoter in T cells. Also, FOG-1 overexpression during primary activation of naive T cells inhibited Th2 development in CD4+ T cells. FOG-1 fully repressed GATA-3-dependent Th2 development and GATA-3 autoactivation, but not Stat6-dependent induction of GATA-3. FOG-1 overexpression repressed development of Th2 cells from naive T cells, but did not reverse the phenotype of fully committed Th2 cells. Thus, FOG-1 may be one factor capable of regulating the Th2 development.

L10 ANSWER 5 OF 16 CAPLUS COPYRIGHT 2002 ACS

2001:541415 Document No. 136:274016 Carbon source-dependent transcriptional regulation of the QCR8 gene in Kluyveromyces lactis. Identification of cis-acting regions and trans-acting factors in the KlQCR8 upstream region. Brons, Janynke F.; Dryla, Agnieszka A.; Pluger, Esther B. E.; Vinkenvleugel, Thessa M. F.; Hornig, Nadine C. D.; Grivell, Les A.; Blom, Jolanda (Section for Molecular Biology, University of Amsterdam, Swammerdam Institute for Life Sciences, Amsterdam, 1098 SM, Neth.). Current Genetics, 39(5-6), 311-318 (English) 2001. CODEN: CUGED5. ISSN: 0172-8083. Publisher: Springer-Verlag.

AB The QCR8 gene of the yeast Kluyveromyces lactis is transcriptionally

regulated by the carbon source in the growth medium. Deletion anal. of the KlQCR8 promoter shows that an element located between -144 bp and -113 bp specifically controls induction of QCR8 gene expression on non-fermentable carbon sources. Specific and differential protein-binding to the activating sequence was obsd. with exts. from glucose- and ethanol/glycerol-grown cells. Induction of the reporter gene and protein-binding was dependent on the presence of a functional KlCAT8 gene, suggesting that, in K. lactis, KlCat8p acts in the transcriptional regulation of respiratory function. The activating element contains no other known regulatory sites but two elements required for RNA holoenzyme functioning, raising the intriguing possibility of carbon source-dependent regulation by a subunit of the RNA polymerase holoenzyme in K. lactis.

L10 ANSWER 6 OF 16 MEDLINE DUPLICATE 3
2001357489 Document Number: 21311397. PubMed ID: 11418466. Platelet characteristics in patients with X-linked macrothrombocytopenia because of a novel GATA1 mutation. Freson K; Devriendt K; Matthijs G; Van Hoof A; De Vos R; Thys C; Minner K; Hoylaerts M F; Vermylen J; Van Geet C. (Center for Molecular and Vascular Biology, Center for Human Genetics, Department of Pathology, University of Leuven, Belgium. ) BLOOD, (2001 Jul 1) 98 (1) 85-92. Journal code: 7603509. ISSN: 0006-4971. Pub. country: United States. Language: English.

AB A new mutation is described in the X-linked gene GATA1, resulting in macrothrombocytopenia and mild dyserythropoietic features but no marked anemia in a 4-generation family. The molecular basis for the observed phenotype is a substitution of glycine for aspartate in the strictly conserved codon 218 (D218G) of the amino-terminal zinc finger loop of the transcription factor GATA1. Zinc finger interaction studies demonstrated that this mutation results in a weak loss of affinity of GATA1 for its essential cofactor **FOG1**, whereas direct D218G-GATA1 binding to DNA was normal. The phenotypic effects of this mutation in the patients' platelets have been studied. Semiquantitative RNA analysis, normalized for beta-actin messenger RNA, showed extremely low transcription of the GATA1 target genes GPIbbeta and GPIX but also a significantly lower expression of the nondirectly GATA1-regulated Gsalpha gene, suggestive of incomplete megakaryocyte maturation. In contrast, GPIIIa expression was close to normal in agreement with its early appearance during megakaryocyte differentiation. Flow cytometric analysis of patient platelets confirmed the existence of a platelet population with abnormal size distribution and reduced GPIb complex levels but with normal GPIIIa expression. It also showed the presence of very immature platelets lacking almost all membrane glycoproteins studied (GPIbalpha, GPIbbeta, GPIIIa, GPIX, and GPV). Patients' platelets showed weak ristocetin-induced agglutination, compatible with the disturbed GPIb complex. Accordingly, electron microscopy of the patients' platelets revealed giant platelets with cytoplasmic clusters consisting of smooth endoplasmic reticulum and abnormal membrane complexes. In conclusion, GATA1 mutations can lead to isolated X-linked macrothrombocytopenia without anemia.

L10 ANSWER 7 OF 16 CAPLUS COPYRIGHT 2002 ACS
2001:358387 Document No. 135:29785 Cell fate in the c. elegans germline is regulated by the CPEB protein fog-1. Jin, Suk-Won (Univ. of Michigan, Ann Arbor, MI, USA). 209 pp. Avail. UMI, Order No. DA9977183 From: Diss. Abstr. Int., B 2001, 61(7), 3423 (English) 2000.

AB Unavailable

L10 ANSWER 8 OF 16 CAPLUS COPYRIGHT 2002 ACS
2000:775894 Document No. 135:1786 CPEB proteins control two key steps in spermatogenesis in Caenorhabditis elegans. Luitjens, Cameron; Gallegos, Maria; Kraemer, Brian; Kimble, Judith; Wickens, Marvin (Program in Cell and Molecular Biology, University of Wisconsin, Madison, WI, 53706, USA). Genes & Development, 14(20), 2596-2609 (English) 2000. CODEN: GEDEEP.

ISSN: 0890-9369. Publisher: Cold Spring Harbor Laboratory Press.

AB Cytoplasmic polyadenylation element binding (CPEB) proteins bind to and regulate the translation of specific mRNAs. CPEBs from Xenopus, Drosophila, and Spisula participate in oogenesis. In this report, we examine the biol. roles of all identifiable CPEB homologs in a single organism, Caenorhabditis elegans. We find four homologs in the C. elegans genome: cbp-1, cpb-2, cpb-3, and fog-1. Surprisingly, two homologs, CPB-1 and FOG-1, have key functions in spermatogenesis and are dispensable for oogenesis. CPB-2 and CPB-3 also appear not to be required for oogenesis. CPB-1 is essential for progression through meiosis: cpb-1(RNAi) spermatocytes fail to undergo the meiotic cell divisions. CPB-1 protein is present in the germ line just prior to overt spermatogenesis; once sperm differentiation begins, CPB-1 disappears. CPB-1 phys. interacts with FBF, another RNA-binding protein and 3' UTR regulator. In addn. to its role in controlling the sperm/oocyte switch, we find that FBF also appears to be required for spermatogenesis, consistent with its interaction with CPEB. A second CPEB homolog, FOG-1, is required for specification of the sperm fate. The fog-1 gene produces fog-1(L) and fog-1(S) transcripts. The fog-1(L) RNA is enriched in animals making sperm and is predicted to encode a larger protein; fog-1(S) RNA is enriched in animals making oocytes and is predicted to encode a smaller protein. The relative abundance of the two mRNAs is controlled temporally during germ-line development and by the sex detn. pathway in a fashion that suggests that the fog-1(L) species encodes the active form. In sum, our results demonstrate that, in C. elegans, two CPEB proteins have distinct functions in the germ line, both in spermatogenesis: FOG-1 specifies the sperm cell fate and CPB-1 executes that decision.

L10 ANSWER 9 OF 16 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.

2001:311956 Document No.: PREV200100311956. Platelet characteristics in patients with X-linked macrothrombocytopenia due to a novel GATA-1 mutation. Freson, Kathleen (1); Devriendt, Koen; Matthijs, Gert; Van Hoof, Achiel; De Vos, Rita; Thys, Chantal; Minner, Kristien; Hoylaerts, Marc F.; Vermylen, Jos; Van Geet, Chris. (1) Center for Molecular and Vascular Biology, University of Leuven, Leuven Belgium. Blood, (November 16, 2000) Vol. 96, No. 11 Part 1, pp. 564a. print. Meeting Info.: 42nd Annual Meeting of the American Society of Hematology San Francisco, California, USA December 01-05, 2000 American Society of Hematology. ISSN: 0006-4971. Language: English. Summary Language: English.

AB GATA1 is the founding member of the GATA-binding family of transcription factors and has been shown to be an essential protein for normal erythropoiesis and megakaryocyte differentiation. Very recently, the first GATA1 genetic defect (V205M) was found in patients with dyserythropoietic anemia and thrombocytopenia (Nat Genet 2000; 24: 266). This single amino acid substitution in GATA1, located in the N-terminal zinc finger, abrogates the interaction with its essential transcription cofactor **FOG1**. We describe a new mutation in the X-linked gene GATA1, resulting in macrothrombocytopenia and mild dyserythropoietic features but no marked anemia in a four-generation family. The molecular basis for the observed phenotype is a substitution of glycine for aspartate in the strictly conserved codon 218 (D218G) of the amino-terminal zinc finger loop of the transcription factor GATA1. We have studied the phenotypic effects of this mutation in the patients' platelets. Semi-quantitative RNA studies, normalized for betaactin mRNA, show extremely low transcription of the GATA1-target genes GPIbbeta and GPIX but also a significantly lower expression of a non GATA1-target gene, Gsalpha. The highly elevated patient platelet RNA content and the weak expression of GPIbbeta and GPIX, normally expressed during late megakaryocyte differentiation, are suggestive of incomplete maturation. In contrast, GPIIIa expression is close to normal in agreement with its early appearance during megakaryocyte differentiation. FACS analysis of patient platelets confirms the existence of a platelet population with abnormal size distribution and

reduced GPIb complex but normal GPIIIa expression, but also shows the presence of immature platelets lacking almost all membrane glycoproteins studied (GPIbalpha, GPIbbeta, GPIIIa, GPIX and GPV). Patient platelets show a weak ristocetin-induced agglutination, compatible with a disturbed GPIb complex. Accordingly, electron microscopy of patient platelets reveals giant platelets with cytoplasmic clusters consisting of smooth endoplasmic reticulum and abnormal membrane complexes.

L10 ANSWER 10 OF 16 MEDLINE DUPLICATE 4
1998350080 Document Number: 98350080. PubMed ID: 9683671. Transcriptional regulation of the KlDLD gene, encoding the mitochondrial enzyme D-lactate ferricytochrome c oxidoreductase in Kluyveromyces lactis: effect of Klhap2 and fog mutations. Lodi T; Goffrini P; Bolondi I; Ferrero I. (Institute of Genetics, University of Parma, Viale delle Scienze, I-43100 Parma, Italy.. tlodi@ipruniv.cce.unipr.it) . CURRENT GENETICS, (1998 Jul) 34 (1) 12-20. Journal code: 8004904. ISSN: 0172-8083. Pub. country: United States. Language: English.

AB Expression of the Kluyveromyces lactis KlDLD gene, encoding the mitochondrial enzyme D-lactate ferricytochrome c oxidoreductase (D-LCR), is subject to two metabolic controls at the transcriptional level: induction by lactate, the substrate of the D-LCR enzyme, and repression by glucose. By Northern analysis we determined the kinetics of the two regulatory processes and, by measurement of the expression of LacZ gene fused to the KlDLD promoter, we identified cis-elements involved in glucose repression and lactate induction. The effect of trans-acting factors on the transcription of KlDLD has been analyzed. The KlDLD gene is controlled by the products of the **FOG1** and FOG2 genes, previously identified as involved in glucose de-repression. Moreover, the KlDLD gene is regulated by the product of KlHAP2, homologous to the HAP2 gene which in Saccharomyces cerevisiae is required for the induction of genes encoding mitochondrial components, upon shifting from a fermentable to a non-fermentable carbon source. We have demonstated that the KlHAP2 gene is necessary both for the lactate induction of KlDLD mRNA synthesis and for growth on this oxidative carbon source.

L10 ANSWER 11 OF 16 MEDLINE DUPLICATE 5
96171514 Document Number: 96171514. PubMed ID: 8598052. **FOG1** and FOG2 genes, required for the transcriptional activation of glucose-repressible genes of Kluyveromyces lactis, are homologous to GAL83 and SNF1 of saccharomyces cerevisiae. Goffrini P; Ficarelli A; Donnini C; Lodi T; Puglisi P P; Ferrero I. (Istituto di Genetica, Universita di Parma, Viale delle Scienze, Italy. ) CURRENT GENETICS, (1996 Mar) 29 (4) 316-26. Journal code: 8004904. ISSN: 0172-8083. Pub. country: United States. Language: English.

AB The **fog1** and fog2 mutants of the yeast Kluyveromyces lactis were identified by inability to grow on a number of both fermentable and non-fermentable carbon sources. Genetic and physiological evidences suggest a role for **FOG1** and FOG2 in the regulation of glucose-repressible gene expression in response to a glucose limitation. The regulatory effect appears to be at the transcriptional level, at least for beta-galactosidase. Both genes have been cloned by complementation and sequenced. **FOG1** is a unique gene homologous to GAL83, SIP1 and SIP2, a family of regulatory genes affecting glucose repression of the GAL system in Saccharomyces cerevisiae. However, major differences exist between **fog1** and gal83 mutants. FOG2 is structurally and functionally homologous to SNF1 of S. cerevisiae and shares with SNF1 a role also in sporulation.

L10 ANSWER 12 OF 16 CAPLUS COPYRIGHT 2002 ACS
1996:151332 Document No. 124:227180 The fog-3 gene and regulation of cell fate in the germ line of Caenorhabditis elegans. Ellis, Ronald E.; Kimble, Judith (Laboratory of Molecular Biology, University of Wisconsin,

Madison, WI, 53706, USA). Genetics, 139(2), 561-77 (English) 1995. CODEN: GENTAE. ISSN: 0016-6731. Publisher: Genetics Society of America.

AB In the nematode Caenorhabditis elegans, germ cells normally adopt one of three fates: mitosis, spermatogenesis or oogenesis. The authors have identified and characterized the gene fog-3, which is required for germ cells to differentiate as sperm rather than as oocytes. Anal. of double mutants suggests that fog-3 is absolutely required for spermatogenesis and acts at the end of the regulatory hierarchy controlling sex detn. for the germ line. By contrast, mutations in fog-3 do not alter the sexual identity of other tissues. The authors also have characterized the null phenotype of fog-1, another gene required for spermatogenesis; the authors demonstrate that it too controls the sexual identity of germ cells but not of other tissues. Finally, the authors have studied the interaction of these two fog genes with gld-1, a gene required for germ cells to undergo oogenesis rather than mitosis. On the basis of these results, the authors propose that germ-cell fate might be controlled by a set of inhibitory interactions among genes that specify one of three fates: mitosis, spermatogenesis or oogenesis. Such a regulatory network would link the adoption of one germ-cell fate to the suppression of the other two.

L10 ANSWER 13 OF 16 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.DUPLICATE 6

90127233 EMBASE Document No.: 1990127233. Cloning of a species-specific DNA probe from Onchocera gibsoni. Garate T.; Harnett W.; Parkhouse R.M.E.. National Institute for Medical Research, Mill Hill, London NW7 1AA, United Kingdom. International Journal for Parasitology 20/1 (31-35) 1990. ISSN: 0020-7519. CODEN: IJPYBT. Pub. Country: United Kingdom. Language: English. Summary Language: English.

AB Cloning of a species-specific DNA probe from Onchocerca gibsoni. International Journal for Parasitology 20: 31-35. A genomic library of Onchocerca gibsoni has been prepared in the vector lambda-gt10 and has been screened for specific DNA sequences by hybridization with radiolabelled total genomic DNA from a number of Onchocerca species. A clone-**fOG1**-has been isolated which does not interact with DNA prepared from O. gutturosa, O. lienalis, O. ochengi, O. cervicalis or O. volvulus (both Liberian and Mexican isolates). In addition, no hybridization is observed with host (cattle) DNA. **fOG1** can detect as little as 100-200 pg of O. gibsoni DNA. It is thus concluded that **fOG1** has the sensitivity to detect microfilariae of O. gibsoni found in the skin of cattle and the specificity to differentiate them from closely related species living in the same environment.

L10 ANSWER 14 OF 16 CAPLUS COPYRIGHT 2002 ACS

1990:510217 Document No. 113:110217 Fog-1, a regulatory gene required for specification of spermatogenesis in the germ line of Caenorhabditis elegans. Barton, M. Kathryn; Kimble, Judith (Coll. Agric. Life Sci., Univ. Wisconsin, Madison, WI, 53706, USA). Genetics, 125(1), 29-39 (English) 1990. CODEN: GENTAE. ISSN: 0016-6731.

AB In wild-type C. elegans, the XO male germ line makes only sperm and the XX-hermaphrodite germ line makes sperm and then oocytes. In contrast, the germ line of either a male or a hermaphrodite carrying a mutation of the fog-1 (feminization of the germ line) locus is sexually transformed: cells that would normally make sperm differentiate as oocytes. However, the somatic tissues of fog-1 mutants remain unaffected. All fog-1 alleles identified confer the same phenotype. The fog-1 mutations reduce fog-1 function, indicating that the wild-type fog-1 product is required for specification of a germ cell as a spermatocyte. Two lines of evidence indicate that a germ cell is detd. for sex at about the same time that it enters meiosis. These include the fog-1 temp.-sensitive period, which coincides in each sex with first entry into meiosis, and the phenotype of a fog-1; glp-1 double mutant. Expts. with double mutants show that fog-1 is epistatic to mutations in all other sex-detg. genes tested. Thus, fog-1 acts as the same level as the fem genes at the end of the sex detn.

pathway to specify germ cells as sperm.

L10 ANSWER 15 OF 16 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
1989:269989 Document No.: BA88:6071. HISTOENZYMATIC CHARACTERISTICS AND THE SIZE OF SKELETAL MUSCLE FIBERS IN THE GUINEA FOWL NUMIDA-MELEAGRIS. MANABE N; SATO E; IZUMI T; ISHIBASHI T. DEP. ANIM. SCI., FAC. AGRICULTURE, KYOTO UNIV., KITASHIRAKAWA, SAKYO-KU, KYOTO 606.. JPN J ORNITHOL, (1988) 37 (1), 1-16. CODEN: JJOREH. Language: Japanese.

AB The myofiber type profiles of the following skeletal muscles of the Guinea Fowl were examined histochemically: M. obliquus externus abdominis, M. obliquus internus abdominis, M. trapezius, M. latissimus dorsi, M. pectralis profundus, M. triceps brachii, M. extensor carpi radialis longus, M. sartorius, M. rectus femoris, M. adductor magnus, M semitendinosus, M. semimembranosus, M. gastrocnemius-caput latelare, M. gastrocnemius-caput mediale, and M. soleus. According to the histoenzymatic reaction pattern (succinate dehydrogenase, malate dehydrogenase, nicotinamide adenine dinucleotide tetrazolium reductase, lactate dehydrogenase, beta hydroxybutylate dehydrogenase, alpha glycerophosphate dehydrogenase, aldolase, phosphorylase, and myosin adenosine triphosphatase), myofibers were divided into three types, i.e. fast-twitch-glycolytic (FG), fast-twitch-oxidative-glycolytic (FOG) and slow-twitch-oxidative (SO) types. Furthermore, according to the intensity of the enzyme reactions, FG type fibers were subdivided into two types, FOG type fibers into four types, and SO type fibers into three types. FG1, FOG2, FOG3, SO1 and SO3 type fibers could be observed in M. obliquus externus abdominis. FG2 FOG2, FOG3, SO1 and SO2 were observed in M. obliquus internus abdominis. SO1 and SO2 were observed in trapezius. FG1, FOG2, FOG3, SO1 and SO2 were observed in M. lattissimus dorsi. FG1, FOG3, FOG4 and SO2 were observed in M. pectralis superficialis, M. pectralis profundud and M. semitendinosus. FG1, FOG3 and SO2 were observed in M. triceps brachii and M. extensor carpi radialis longus. FG1, **FOG1** , FOG3, SO1 and SO2 were observed in M. sartorius and M. rectus femoris. FG2, FOG2, FOG3 and SO1 were observed in M. adductor magnus. FG2, FOG2, FOG3, SO2 and SO3 were observed in M. semimembranosus. FG1, **FOG1** , FOG2 and SO1 were observed in M. gastrocnemius-caput raterale and mediale. FG2, FOG2, FOG3, SO1 and SO2 were observed in M. soleus. The ratio of the number of the FG type fibers was higher than the fibers of other types with exception of M. obliquus externus abdominis, M. obliquus internus abdominis, M. rectus femoris, M. adductor magnus, M. semimembranosus and M. soleus. In these exceptional muscles, FOG type fibers were dominant. M. trapezius was composed of SO type fibers. The diameter of myofiber showed the largest value in FG type fibers with the exception of M. trapezius and M. soleus, and showed the smallest value in SO type fibers with the exception of M. trapezius, M. adductor magnus, M. semimembranosus, M. gastrocnemius-caput latelare, M. gastrocnemius-caput mediale and M. soleus. The variation of myofiber was largest in FG type fibers. The pH stability of myosin ATPase activity varies with the muscle fiber types. The range of pH stability of alkaline pH range was more extensive in FG type fibers than in the other types of myofiber, whereas at acidic pH range SO type fibers were more extensive in the range of pH stability than other myofiber types.

L10 ANSWER 16 OF 16 CAPLUS COPYRIGHT 2002 ACS
1984:129801 Document No. 100:129801 Silver halide color photographic photosensitive material. Kato, Kazuo; Watanabe, Yoshikazu; Kumashiro, Kenji; Shimba, Satoru (Konishiroku Photo Industry Co., Ltd. , Japan). Eur. Pat. Appl. EP 85580 A1 19830810, 80 pp. DESIGNATED STATES: R: DE, FR, GB. (English). CODEN: EPXXDW. APPLICATION: EP 1983-300533 19830202. PRIORITY: JP 1982-16667 19820203.

GI For diagram(s), see printed CA Issue.

AB A color photog. material producing a high max. color d. contains .gtoreq.1 magenta coupler I (R = benzamido, anilino, phenylvreido radical

substituted by sulfonylamino or aminosulfonyl radical; R1 = aryl, heterocyclic radical) and .gtoreq.1 development inhibitor releasing (DIR) compd. contg. a radical II (R2 = H, halogen, acylamino, alkyl, benzothiazolinylidenamino, Ph substituted alkoxy) or III (X = atoms necessary to complete 5- or -6-member ring). Thus, a triacetate film support was coated with a compn. contg. 1 mol of a Ag(Br,I) emulsion contg. 6 mol.% of AgI and 4-hydroxy-6-methyl-1,3,3a,7-tetrazaindene, saponin, 1,2-bis(vinylsulfonyl)ethane, and a mixt. contg. coupler IV 20, DIR compd. V 1 g, tricresyl phosphate 10, EtOAc 50, 10% aq. Alkanol 8 20, 10% aq. gelatin 100 mL, imagewise exposed, color developed in a soln. contg. 4-amino-3-methyl-N-ethyl-N-(.beta.-hydroxyethyl)aniline sulfate 4.75, Na2SO3 4.25, hydroxylamine.1/2 sulfate 2, K2CO3 37.5, KBr 1.3, tri-Na nitrilacetate 2.5, KOH 1 g, H2O to 1 g (pH = 10), bleached, fixed, and stabilized to give an image with max. d. 1.9, relative speed 105, .DELTA.**fog1** and .DELTA.fog2 (values of increase in fog of the sample when processed in the color developer of pH = 10.2 and kept at 40.degree.) 0.04 and 0.04, resp.

```
=> s "CAMPATH-1"
L11       1035 "CAMPATH-1"

=> s l11 and binding domain
L12          1 L11 AND BINDING DOMAIN

=> d l12 cbib abs

L12  ANSWER 1 OF 1  CAPLUS  COPYRIGHT 2002 ACS
1994:52663   Document No. 120:52663  Diphtheria toxin analogs with a modified
     receptor-binding domain.  Choe, Seunghyon; Eisenberg,
     David; Genbauffe, Francis S., Jr. (University of California, USA; Seragen,
     Inc.).  PCT Int. Appl. WO 9322450 A1 19931111, 115 pp.  DESIGNATED STATES:
     W:  AT, AU, BB, BG, BR, CA, CH, CZ, DE, DK, ES, FI, GB, HU, JP, KP, KR,
     LK, LU, MG, MN, MW, NL, NO, NZ, PL, PT, RO, RU, SD, SE, SK, UA, VN; RW:
     AT, BE, BF, BJ, CF, CG, CH, CI, CM, DE, DK, ES, FR, GA, GB, GR, IE, IT,
     LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG.  (English).  CODEN: PIXXD2.
     APPLICATION: WO 1993-US4335 19930507.  PRIORITY: US 1992-879630 19920507.
AB   A diphtheria toxin mol. with part or all of an antibody complementarity
     detg. region inserted into a loop region of the diphtheria toxin receptor
     binding-domain is described.  The protein is for use as
     an immunotoxin (no data).  The inserted sequence may be more complex than
     a single complementarity-detg. region and may be any other protein showing
     specific binding, such as tumor necrosis factor.  The structure of a
     fusion protein of the diphtheria toxin capable of recognizing the
     Campath-1 antigen was detd. by X-ray crystallog.  The
     chimeric gene for the fusion protein was constructed and expressed by std.
     methods.

=> s "FOG-1 domain"
L13          0 "FOG-1 DOMAIN"

=> s IgG
L14     304994 IGG

=> s l14 and CH2 domain
L15        429 L14 AND CH2 DOMAIN

=> s l15 and amino acid substitution
L16         23 L15 AND AMINO ACID SUBSTITUTION

=> dup remove l16
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PROCESSING COMPLETED FOR L16
L17 10 DUP REMOVE L16 (13 DUPLICATES REMOVED)

=> d l17 1-10 cbib abs

L17 ANSWER 1 OF 10 CAPLUS COPYRIGHT 2002 ACS
2002:329048 Alefacept, an immunomodulatory recombinant LFA-3/IgG1 fusion protein, induces CD16 signaling and CD2/CD16-dependent apoptosis of CD2+ cells. Da Silva, Antonio J.; Brickelmaier, Margot; Majeau, Gerard R.; Li, Zhifang; Su, Lihe; Hsu, Yen-Ming; Hochman, Paula S. (Biogen, Inc., Cambridge, MA, 02142, USA). Journal of Immunology, 168(9), 4462-4471 (English) 2002. CODEN: JOIMA3. ISSN: 0022-1767. Publisher: American Association of Immunologists.

AB Alefacept, an immunomodulatory recombinant fusion protein composed of the first extracellular domain of LFA-3 fused to the human IgG1 hinge, CH2, and CH3 domains, has recently been shown in phase II and III clin. trials to safely reduce disease expression in patients with chronic plaque psoriasis. Alefacept modulates the function of and selectively induces apoptosis of CD2+ human memory-effector T cells in vivo. We have sought to gain further understanding of the mechanisms of action that influence the biol. activity of alefacept and may contribute to its efficacy and patient responsiveness. Specifically evaluated is the ability of alefacept to activate intracellular signals mediated via CD2 and/or Fc.gamma.RIII (CD16). Experimentation using isoforms of alefacept engineered to have **amino acid substitutions** in the IgG1 **CH2 domain** that impact Fc.gamma.R binding indicate that alefacept mediates cognate interactions between cells expressing human CD2 and CD16 to activate cells, e.g., increase extracellular signal-regulated kinase phosphorylation, up-regulate cell surface expression of the activation marker CD25, and induce release of granzyme B. In the systems used, this signaling is shown to require binding to CD2 and CD16 and be mediated through CD16, but not CD2. Experimentation using human CD2-transgenic mice and isoforms of alefacept confirmed the requirement for Fc.gamma.R binding for detection of the pharmacol. effects of alefacept in vivo. Thus alefacept acts as an effector mol., mediating cognate interactions to activate Fc.gamma.R+ cells (e.g., NK cells) to induce apoptosis of sensitive CD2+ target cells.

L17 ANSWER 2 OF 10 MEDLINE
2002114858 Document Number: 21838713. PubMed ID: 11849310. IgG4 breaking the rules. Aalberse Rob C; Schuurman Janine. (Department of Immunopathology, CLB, Amsterdam, The Netherlands.. aalberse@clb.nl) . IMMUNOLOGY, (2002 Jan) 105 (1) 9-19. Ref: 66. Journal code: 0374672. ISSN: 0019-2805. Pub. country: England: United Kingdom. Language: English.

AB Immunoglobulin G4 (IgG4) antibodies have been known for some time to be functionally monovalent. Recently, the structural basis for this monovalency has been elucidated: the in vivo exchange of **IgG** half-molecules (one H-plus one L-chain) among IgG4. This process results in bispecific antibodies that in most situations will behave as functionally monovalent antibodies. The structural basis for the abnormal behaviour of IgG4 seems to be largely the result of a single amino acid change relative to human IgG1: the change of a proline in core hinge of IgG1 to serine. This results in a marked shift in the equilibrium between interchain disulphide bridges and intrachain disulphide bridges, which for IgG4 results in 25-75% absence of a covalent interaction between the H-chains. Because of strong non-covalent interactions between the CH3 domains (and possibly also between the CH1 domain and the trans-**CH2 domain**) IgG4 is a stable four-chain molecule and does not easily exchange half-molecules under standard physiological conditions in vitro. We postulate that the exchange is catalysed in vivo by protein disulphide isomerase (PDI) and/or FcRn (the major histocompatibility complex (MHC)-related Fc receptor) during transit of

IgG4 in the endosomal pathway in endothelial cells. Because IgG4 is predominantly expressed under conditions of chronic antigen exposure, the biological relevance of this exchange of half-molecules is that it generates antibodies that are unable to form large immune complexes and therefore have a low potential for inducing immune inflammation. In contrast to monovalent immunoglobulin fragments, these scrambled immunoglobulins have a normal half-life. The significance of the ensuing bispecificity needs further evaluation, because this will be relevant only in situations where high IgG4 responses are found to two unrelated antigens that happen to be present in the body at the same time and place. In this context the significance of IgG4 autoreactivity might have to be re-evaluated. The main function of IgG4, however, is presumably to interfere with immune inflammation induced by complement-fixing antibodies, or, in the case of helminth infection or allergy, by IgE antibodies.

L17 ANSWER 3 OF 10 MEDLINE

2001181568 Document Number: 21112159. PubMed ID: 11161972. Modification of the Fc region of a primatized **IgG** antibody to human CD4 retains its ability to modulate CD4 receptors but does not deplete CD4(+) T cells in chimpanzees. Newman R; Hariharan K; Reff M; Anderson D R; Braslawsky G; Santoro D; Hanna N; Bugelski P J; Brigham-Burke M; Crysler C; Gagnon R C; Dal Monte P; Doyle M L; Hensley P C; Reddy M P; Sweet R W; Truneh A. (IDEC Pharmaceuticals Corporation, 11011 Torreyana Road, San Diego, California, 92121, USA. ) CLINICAL IMMUNOLOGY, (2001 Feb) 98 (2) 164-74. Journal code: 100883537. ISSN: 1521-6616. Pub. country: United States. Language: English.

AB Keliximab, a Primatized IgG1 CD4 mAb, was reconfigured to an IgG4 antibody. The gamma4 constant region was further modified by substituting glutamic acid for serine at position 235 in the **CH2 domain** (IgG4-E), to remove residual binding to Fcgamma receptors, and substitution of serine with proline at position 228 in the hinge region (IgG4-PE) for greater stability. Pharmacokinetic analysis in rats gave a t(1/2) of approximately 4 days for IgG4-E and 9 days for IgG4-PE, consistent with a greater stability of the IgG4-PE molecule. The effects on T cell subsets were assessed in chimpanzees given escalating doses of IgG4-PE: 0.05 mg/kg on Day 16, 1.5 mg/kg dose on Day 43, and 15 mg/kg on Day 85. Receptor modulation was observed at the two highest doses, but no depletion of T cells at any dose. The in vitro and in vivo results demonstrate the potential of this IgG4-PE mAb for use in human trials. 

L17 ANSWER 4 OF 10 MEDLINE DUPLICATE 1

2000150830 Document Number: 20150830. PubMed ID: 10688122. Single **amino acid substitution** in the Fc region of chimeric TNT-3 antibody accelerates clearance and improves immunoscintigraphy of solid tumors. Hornick J L; Sharifi J; Khawli L A; Hu P; Bai W G; Alauddin M M; Mizokami M M; Epstein A L. (Department of Pathology, University of Southern California School of Medicine, Los Angeles 90033, USA. ) JOURNAL OF NUCLEAR MEDICINE, (2000 Feb) 41 (2) 355-62. Journal code: 0217410. ISSN: 0161-5505. Pub. country: United States. Language: English.

AB Recent studies in antibody catabolism have identified residues at the CH2-CH3 interface of the **IgG** heavy chain critical for serum persistence of immunoglobulins. **Amino acid substitutions** in the Fc region of murine IgG1 were shown to drastically accelerate antibody clearance in mice. Our laboratory has previously described a human-mouse chimeric TNT-3 (chTNT-3) monoclonal antibody directed against a universal nuclear antigen that has potential for the radioimmunotherapy of many solid tumors. In the current study, we engineered a chTNT-3 mutant containing a single **amino acid substitution**, to determine whether a more rapid

clearance profile would make the antibody suitable for diagnostic imaging. METHODS: A single **amino acid substitution** in the **CH2 domain** of the human gamma1 constant region was made by polymerase chain reaction mutagenesis. High-level expression was achieved using the Glutamine Synthetase Gene Amplification System, and the chTNT-3 mutant was purified by protein A affinity and ion-exchange chromatography. A radioimmunoassay was performed to examine antigen binding, and in vivo studies were undertaken to evaluate clearance and tumor targeting in human tumor xenograft models. RESULTS: The chTNT-3 mutant retained the high affinity of chTNT-3, with a binding constant of 1.5 x 10(-9) mol/L. The mutant was eliminated rapidly from BALB/c mice, with a beta-phase half-life of 33.8 h, compared to 134.2 h for chTNT-3. Moreover, biodistribution studies in human colon tumor-bearing nude mice reflected this accelerated clearance. Tumor levels of the mutant were, respectively, 65%, 39%, and 36% of the tumor levels achieved with the parental chTNT-3 6, 12, and 24 h postinjection. The rapid clearance of the chTNT-3 mutant from the blood resulted in higher tumor-to-normal organ ratios for many normal tissues. Imaging of tumor-bearing mice with 99mTc-labeled chTNT-3 mutant demonstrated early visualization of tumors in 3 different solid tumor xenograft models. CONCLUSION: The accelerated clearance produced by a single **amino acid substitution** in the Fc region of chTNT-3 leads to improved imaging in tumor-bearing mice. These studies suggest that a rapidly clearing antibody generated by this approach may be useful for the immunoscintigraphy of human tumors.

L17 ANSWER 5 OF 10 MEDLINE

1999388014 Document Number: 99388014. PubMed ID: 10458776. Recombinant human **IgG** molecules lacking Fcgamma receptor I binding and monocyte triggering activities. Armour K L; Clark M R; Hadley A G; Williamson L M. (Division of Immunology Department of Pathology, University of Cambridge, Cambridge, GB. ) EUROPEAN JOURNAL OF IMMUNOLOGY, (1999 Aug) 29 (8) 2613-24. Journal code: 1273201. ISSN: 0014-2980. Pub. country: GERMANY: Germany, Federal Republic of. Language: English.

AB Subclasses of human **IgG** have a range of activity levels with different effector systems but each triggers at least one mechanism of cell destruction. We are aiming to engineer non-destructive human **IgG** constant regions for therapeutic applications where depletion of cells bearing the target antigen is undesirable. The attributes required are a lack of killing via Fcgamma receptors (R) and complement but retention of neonatal FcR binding to maintain placental transport and the prolonged half-life of **IgG**. Eight variants of human **IgG** constant regions were made with anti-RhD and CD52 specificities. The mutations, in one or two key regions of the **CH2 domain**, were restricted to incorporation of motifs from other subclasses to minimize potential immunogenicity. IgG2 residues at positions 233 - 236, substituted into IgG1 and IgG4, reduced binding to FcgammaRI by 10(4)-fold and eliminated the human monocyte response to antibody-sensitized red blood cells, resulting in antibodies which blocked the functions of active antibodies. If glycine 236, which is deleted in IgG2, was restored to the IgG1 and IgG4 mutants, low levels of activity were observed. Introduction of the IgG4 residues at positions 327, 330 and 331 of IgG1 and IgG2 had no effect on FcgammaRI binding but caused a small decrease in monocyte triggering.

L17 ANSWER 6 OF 10 MEDLINE DUPLICATE 2

92178230 Document Number: 92178230. PubMed ID: 1542298. Blood clearance in the rat of a recombinant mouse monoclonal antibody lacking the N-linked oligosaccharide side chains of the **CH2 domains**. Wawrzynczak E J; Cumber A J; Parnell G D; Jones P T; Winter G. (Drug Targeting Laboratory, Section of Medicine, Institute of Cancer Research, Sutton, Surrey, U.K. ) MOLECULAR IMMUNOLOGY, (1992 Feb) 29 (2) 213-20.

Journal code: 7905289. ISSN: 0161-5890. Pub. country: ENGLAND: United Kingdom. Language: English.

AB The serum half-lives of a wild-type recombinant mouse monoclonal antibody of the IgG2b isotype and a mutant antibody differing from the wild-type antibody by a single **amino acid substitution** introduced into the **CH2 domain**, the replacement of Asn 297 by Ala to delete the conserved site of heavy chain glycosylation, were determined in the rat. The biological half-life of the aglycosyl Asn 297-Ala mutant recombinant antibody (4.8 days) was significantly shorter than that of the normally glycosylated wild-type antibody (7.4 days) by enzyme immunoassay. A similar difference between the biological half-lives of 125I-labelled aglycosyl and wild-type antibodies (2.9 and 4.0 days, respectively) was determined by gamma counting. Analysis of serum samples demonstrated that both recombinant antibodies were present in the circulation predominantly as intact monomeric **IgG** and revealed no differences that could account for the more rapid elimination of the aglycosyl antibody. The results of this investigation indicate that the carbohydrate residues contribute only in part to the survival of **IgG** in vivo and suggest that the diminished half-life of the aglycosyl antibody is due to increased catabolism in the extravascular tissues.

L17 ANSWER 7 OF 10 MEDLINE DUPLICATE 3

92020986 Document Number: 92020986. PubMed ID: 1833770. Identification of the Fc gamma receptor class I binding site in human **IgG** through the use of recombinant IgG1/IgG2 hybrid and point-mutated antibodies. Chappel M S; Isenman D E; Everett M; Xu Y Y; Dorrington K J; Klein M H. (Department of Immunology, University of Toronto, ON, Canada. ) PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA, (1991 Oct 15) 88 (20) 9036-40. Journal code: 7505876. ISSN: 0027-8424. Pub. country: United States. Language: English.

AB To characterize the region on human IgG1 responsible for its high-affinity interaction with the human Fc gamma receptor class I (Fc gamma RI), we have analyzed the binding properties of a series of genetically engineered chimeric antidinitrophenyl antibodies with identical murine antibody combining sites and hybrid IgG1/IgG2 human constant (C) regions. In addition, we have investigated a panel of reciprocally point-mutated IgG1 and IgG2 chimeric antibodies to identify the amino acid residues that confer cytophilic properties to human IgG1. Our data unambiguously indicate that cytophilic activity of IgG1 is an intrinsic property of its heavy-chain C region 2 (**CH2**) **domain**. We report that the entire sequence spanning residues 234-237 (LLGG) is required to restore full binding activity to IgG2 and IgG4 and that individual **amino acid substitutions** failed to render IgG2 active. Nevertheless, the reciprocal single point mutations in IgG1 either significantly lowered its activity or abolished it completely. Finally, we observed that an IgG2 antibody containing the entire ELLGGP sequence (residues 233-238) was more active than wild-type IgG1. This finding suggests that in addition to the primary contact site identified in the N terminus of the gamma 1 **CH2 domain**, secondary sites involving residues from the C-terminal half of the domain may also contribute to the IgG1-Fc gamma RI interaction.

L17 ANSWER 8 OF 10 MEDLINE DUPLICATE 4

91237294 Document Number: 91237294. PubMed ID: 1827828. The binding affinity of human **IgG** for its high affinity Fc receptor is determined by multiple amino acids in the **CH2 domain** and is modulated by the hinge region. Canfield S M; Morrison S L. (Department of Microbiology, Columbia University, College of Physicians and Surgeons, New York, New York 10032. ) JOURNAL OF EXPERIMENTAL MEDICINE, (1991 Jun 1) 173 (6) 1483-91. Journal code: 2985109R. ISSN: 0022-1007. Pub. country: United States. Language: English.

AB A family of chimeric immunoglobulins (Igs) bearing the murine variable region directed against the hapten dansyl linked to human IgG1, -2, -3, and -4 has been characterized with respect to binding to the human high affinity Fc gamma receptor, Fc gamma RI. Chimeric IgG1 and -3 have the highest affinity association (Ka = 10(9) M-1), IgG4 is 10-fold reduced from this level, and IgG2 displays no detectable binding. A series of genetic manipulations was undertaken in which domains from the strongly binding subclass IgG3 were exchanged with domains from the nonbinding subclass IgG2. The subclass of the **CH2 domain** was found to be critical for determining **IgG** receptor affinity. In addition, the hinge region was found to modulate the affinity of the **IgG** for Fc gamma RI, possibly by determining accessibility of Fc gamma RI to the binding site on Fc. A series of **amino acid substitutions** were engineered into the **CH2 domain** of IgG3 and IgG4 at sites considered potentially important to Fc receptor binding based on homology comparisons of binding and nonbinding **IgG** subclasses. Characterization of these mutants has revealed the importance for Fc gamma RI association of two regions of the genetic **CH2 domain** separated in primary structure by nearly 100 residues. The first of these is the hinge-link or lower hinge regions, in which two residues, Leu (234) and Leu(235) in IgG1 and -3, are critical to high affinity binding. Substitution at either of these sites reduces the **IgG** association constant by 10-100-fold. The second region that appears to contribute to receptor binding is in a hinge-proximal bend between two beta strands within the **CH2 domain**, specifically, Pro(331) in IgG1 and -3. As a result of beta sheet formation within this domain, this residue lies within 11 A of the hinge-link region. Substitution at this site reduces the Fc receptor association constant by 10-fold.

L17 ANSWER 9 OF 10 CAPLUS COPYRIGHT 2002 ACS
1989:207251 Document No. 110:207251 Altered antibodies having altered effector functions and their preparation. Winter, Gregory Paul; Duncan, Alexander Robert; Burton, Dennis Raymond (Medical Research Council, UK). PCT Int. Appl. WO 8807089 A1 19880922, 42 pp. DESIGNATED STATES: W: AU, GB, JP, US; RW: AT, BE, CH, DE, FR, GB, IT, LU, NL, SE. (English). CODEN: PIXXD2. APPLICATION: WO 1988-GB211 19880318. PRIORITY: GB 1987-6425 19870318; GB 1987-18897 19870810; GB 1987-28042 19871201.
AB Antibodies (Ab) with altered binding affinity for effectors such as the Clq component of the complement system are prepd. by replacing amino acid residues of the CH2 region using genetic engineering techniques. Human C.gamma.3 genes having a mutation, i.e. 234-leucine to alanine, 235-leuciner to glutamine, 236-glycine to alanine, and 237-glycine to alanine, resp., were constructed and cloned into expression vector pSBgpt after linking with the gene encoding the variable domain of the B18 antibody (Ab). The binding affinity I50 (the concn. of IgG3 at which the fractional binding of 125I-labeled pooled human **IgG** is 0.5) to Fc .gamma. R1 receptor on U937 cells of the recombinant mutants, i.e. [234-Ala]-IgG3, [235-Glu]-IgG3, [236-Ala]-IgG3, and [237-Ala]-IgG3 were 4 .times. 10-8, >10-6, 3 .times. 10-8, and 3 .times. 10-7M, resp., vs. 10-8M of the control using the wild-type **IgG**.

L17 ANSWER 10 OF 10 MEDLINE DUPLICATE 5
89078461 Document Number: 89078461. PubMed ID: 3060362. Complement activation is not required for **IgG**-mediated suppression of the antibody response. Heyman B; Wiersma E; Nose M. (Department of Immunology, Uppsala University, Sweden. ) EUROPEAN JOURNAL OF IMMUNOLOGY, (1988 Nov) 18 (11) 1739-43. Journal code: 1273201. ISSN: 0014-2980. Pub. country: GERMANY, WEST: Germany, Federal Republic of. Language: English.
AB Feedback suppression of the antibody response by **IgG** is known to be dependent on intact Fc regions. However, it is not clear which of the Fc-mediated effector functions is required. In the present report we have

studied whether ability or inability of the **IgG** antibodies to activate the complement system was of consequence for their immunosuppressive effect. First, a monoclonal IgG1-anti-2,4,6-trinitrophenyl (TNP) antibody, unable to activate complement via the classical or alternate pathway, was shown to be able to inhibit more than 90% of the in vivo sheep erythrocyte-specific antibody response in mice when TNP coupled to sheep erythrocytes was used as antigen. Second, we investigated the immunosuppressive ability of a non-complement-activating mutant IgG2a-anti-TNP monoclonal antibody. The mutant differs from the wild type by a single **amino acid substitution** in the **CH2 domain** leading to inability to fix complement factor C1q. However, the mutant has the same affinity for antigen and the same Fc receptor-binding capacity as the wild type antibody. It is demonstrated that the mutant was as efficient as the wild type antibody in inhibiting an in vitro antibody response to TNP-coupled sheep erythrocytes. These findings confirm the non-determinant specificity and Fc dependence of **IgG**-mediated suppression, and show that the Fc-mediated effector mechanism is independent of complement activation. The results instead suggest binding to Fc receptors as a necessary step in feedback immunosuppression and favor inactivation of B cells by cross-linking of Fc and antigen receptors on their surface rather than elimination of antigen by complement-dependent phagocytosis as the effector mechanism.

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=> s (armour k?/au or clark m?/U or williamson l?/au)
'U' IS NOT A VALID FIELD CODE
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'U' IS NOT A VALID FIELD CODE
L18       1074 (ARMOUR K?/AU OR CLARK M?/U OR WILLIAMSON L?/AU)

=> s (armour k?/au or clark m?/au or williamson l?/au)
L19      11371 (ARMOUR K?/AU OR CLARK M?/AU OR WILLIAMSON L?/AU)

=> s l19 and immunoglobulin
L20        379 L19 AND IMMUNOGLOBULIN

=> s l20 and "not trigger complement mediated lysis"
L21          1 L20 AND "NOT TRIGGER COMPLEMENT MEDIATED LYSIS"

=> d l21 cbib abs

L21  ANSWER 1 OF 1  CAPLUS  COPYRIGHT 2002 ACS
1999:736770   Document No. 131:350263  Chimeric proteins containing IgG Fc
     fragments which do not trigger complement
     mediated lysis.  Armour, Kathryn Lesley;
     Clark, Michael Ronald; Williamson, Lorna McLeod
     (Cambridge University Technical Services Limited, UK).  PCT Int. Appl. WO
     9958572 A1 19991118, 81 pp.  DESIGNATED STATES: W:  AE, AL, AM, AT, AU,
     AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD,
     GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR,
     LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE,
     SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ,
     BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY,
     DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE,
     SN, TD, TG.  (English).  CODEN: PIXXD2.  APPLICATION: WO 1999-GB1441
     19990507.  PRIORITY: GB 1998-9951 19980508.
AB   The authors disclose recombinant polypeptides comprising: (i) a binding
     domain capable of binding a target mol., and (ii) an effector domain
     having an amino acid sequence substantially homologous to all or part of a
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const. domain of a human **Ig** heavy chain. These chimeric proteins are capable of binding the target mol. without triggering significant complement dependent lysis, or cell mediated destruction of the target and, via the effector domain, remain capable of specifically binding FcRn and/or Fc.gamma.RIIb. These effector domains are derived from two or more human **Ig** heavy chain CH2 domains. The binding domain of the chimeric proteins may be derived from antibodies, enzymes, hormones, receptors, and cytokines etc.

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L22 172 DUP REMOVE L20 (207 DUPLICATES REMOVED)

=> s l15 and anti-fog1
L23 0 L15 AND ANTI-FOG1

=> s l23 and recombinant polypeptide
L24 0 L23 AND RECOMBINANT POLYPEPTIDE

=> s l22 and recombinant polypeptide
L25 1 L22 AND RECOMBINANT POLYPEPTIDE

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L25 ANSWER 1 OF 1 CAPLUS COPYRIGHT 2002 ACS
1999:736770 Document No. 131:350263 Chimeric proteins containing IgG Fc fragments which do not trigger complement mediated lysis. **Armour, Kathryn Lesley; Clark, Michael Ronald; Williamson, Lorna McLeod** (Cambridge University Technical Services Limited, UK). PCT Int. Appl. WO 9958572 A1 19991118, 81 pp. DESIGNATED STATES: W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 1999-GB1441 19990507. PRIORITY: GB 1998-9951 19980508.
AB The authors disclose **recombinant polypeptides** comprising: (i) a binding domain capable of binding a target mol., and (ii) an effector domain having an amino acid sequence substantially homologous to all or part of a const. domain of a human **Ig** heavy chain. These chimeric proteins are capable of binding the target mol. without triggering significant complement dependent lysis, or cell mediated destruction of the target and, via the effector domain, remain capable of specifically binding FcRn and/or Fc.gamma.RIIb. These effector domains are derived from two or more human **Ig** heavy chain CH2 domains. The binding domain of the chimeric proteins may be derived from antibodies, enzymes, hormones, receptors, and cytokines etc.

=> d l22 and chimeric antibody
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'AND' IS NOT A VALID FORMAT
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2002:136066 Document No. 136:182469 High affinity humanized anti-TAG-72 monoclonal antibodies for cancer diagnosis and treatment. Anderson, W. H. Kerr; Tempest, Philip R.; Carr, Frank J.; Harris, William J.; **Armour, Kathryn** (The Dow Chemical Company, USA). U.S. US 6348581 B1 20020219, 40 pp. (English). CODEN: USXXAM. APPLICATION: US 1998-25203 19980218. PRIORITY: US 1996-PV30173 19961031; WO 1997-US19641 19971030.